DEVELOPMENT AND COMMERCIALIZATION OF A BIOABSORBABLE STENT FOR THE TREATMENT OF CONGENITAL HEART DISEASE IN PEDIATRIC PATIENTS

by

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Development and commercialization of a Bioabsorbable Stent for the Treatment of Congenital Heart Disease in Pediatric Patients

Abstract

by

FEHMIDA KAPADIA

Pediaworks is a non-profit organization dedicated to developing pediatric devices to address the market needs of a small niche market with little to no profit potential. Pediaworks identified Arterial Remodeling Technologies (ART) as a potential partner to develop a bioabsorbable pediatric stent (referred to as PediaStent) for the treatment of congenital heart diseases in newborns and children. In collaboration with ART PediaWorks has developed a working prototype of the stent that has been well received by physicians. The stent has demonstrated good potential in adult animal studies. PediaWorks intends to conduct the necessary pre-clinical and clinical studies to get the stents approved by the FDA under Humanitarian Device Exemption (HDE). PediaWorks expects to incur developmental costs of $5mm and have the stents in the market by 2016. At a price point of $5000 per stent, Pediaworks can breakeven by year six and be a sustainable company after that.
1 PediaWorks

PediaWorks is a 501.c.3 non-profit that believes market size should never prevent live-saving ideas from reaching pediatric doctors' hands. Its mission is to develop medical devices which may offer little or no financial return, but will improve the health and welfare of children. By employing a creative business model and network of specialized partners and physicians, PediaWorks is able to circumvent the traditional pediatric market-size barriers and develop solutions. In 2009 PediaWorks' partners BioEnterprise and the Institute of Pediatric Innovation conducted a survey of pediatric cardiologists which revealed that bioresorbable stents were a significant unmet need. PediaWorks identified ART as a potential partner and shortly after instituted a co-development program.
2 Congenital Heart Disease

Congenital Heart Disease (CHD) is a condition present at birth due to the improper development of the heart or its surrounding blood vessels. Every year 36,000 children are born in the US with some form of CHD and many of them do not live to celebrate their first birthday. The main CHDs identified are

Table 2.1: Congenital Heart Diseases and its Incidence

<table>
<thead>
<tr>
<th>Defect</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular Septal Defect (VSD)</td>
<td>30% of all CHDs</td>
</tr>
<tr>
<td>Atrial Septal Defect (ASD)</td>
<td>19% of all CHDs</td>
</tr>
<tr>
<td>Pulmonary Stenosis</td>
<td>10% of all CHDs</td>
</tr>
<tr>
<td>Coarctation of Aorta</td>
<td>6.7% of all CHDs</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>8.6% of all CHDs</td>
</tr>
<tr>
<td>Patent Foramen Ovale</td>
<td>7.5% of all CHDs</td>
</tr>
<tr>
<td>Aortic Valve Stenosis</td>
<td>6.0% of all CHDs</td>
</tr>
<tr>
<td>Patent Ductus Ateriosus</td>
<td>5.5% of all CHDs</td>
</tr>
<tr>
<td>Pulmonary Artery Stenosis</td>
<td>4.2% of all CHDs</td>
</tr>
<tr>
<td>Transposition of great arteries</td>
<td>2.8% of all CHDs</td>
</tr>
</tbody>
</table>

Although CHDs are present at birth, the symptoms may not be visible immediately, for example, in patients suffering from VSD. Some of these defects if minor may never present themselves and the patient can have a healthy normal lifespan, while others will have to be treated. Some CHD’s can be treated
with medication alone and some will require one or more surgeries or interventions. Advances in interventional cardiology have resulted in the development of Percutaneous Transcatheter Devices for the closure of VSD and ASD.

CHD’s associated with stenosis are currently treated by invasive surgical procedures or balloon dilations. Patients undergoing balloon dilations have to undergo repeat procedures every few years as the dilated vessels tend to collapse over time in the absence of a stent to hold them open while they heal. Similarly, patients undergoing surgical intervention might also require multiple procedures depending upon the severity of the disease or due to secondary stenosis occurring in other parts of the vessel over a period of time. Additionally, there is a risk of death associated with surgical procedures. Hence, patients suffering from stenotic CHD’s would greatly benefit if a pediatric stent was available to them. CHD’s associated with stenosis are explained in detail below

2.1 Tetralogy of Fallot (ToF)

ToF is composed of four defects, which include VSD, stenosis or narrowing of the pulmonary outflow tract, ventricular hypertrophy and an overriding aorta. The treatment for this defect is surgical repair when the infant is very young.

Figure 2.1: Tetralogy of Fallot
2.2 Coarctation of Aorta (CoA)

CoA is a narrowing of the aorta, which creates blood pressure gradients and affects blood supply to the body.

Almost 50% of newborns suffering from this defect will exhibit symptoms in the first few days of life and will require surgical intervention. More than 90% of patients are currently treated surgically in the absence of other methods of treatment. Physicians have indicated that they would like to use stents instead of surgical repair to remedy this defect. Bare metal stents are currently being used off-label for the repair of CoA by several physicians across the world.

2.3 Patent Ductus Arteriosus (PDA)

The ductus arteriosus connects the pulmonary artery to the aorta which allows blood to bypass the lungs during fetal development and closes soon after child birth. When the ductus arteriosus fails to close, the condition is called PDA which leads to abnormal blood flow between the aorta and the pulmonary artery. In some
cases the PDA will resolve naturally, but in most cases the physician will have to intervene. Where the physician has to intervene, the treatment of choice is a transcatheter device which seals the opening and restores normal blood flow. PDAs are sometimes associated with artery stenosis which could be repaired with stents.

2.4 Pulmonary Artery Stenosis (PAS)

PAS is a narrowing of the pulmonary or its branch arteries which is present as a single disorder or is associated with other CHD’s like ToF, PDA, truncus arteriosus, pulmonary valve stenosis and pulmonary atresia. As a result of the stenosis blood flow from the heart to the lungs is reduced, which in turn reduces blood flow to the body. Treatment options include balloon dilation, cutting balloons or surgery. As indicated in personal communications with physicians, this would be the most common indication where stenting would be the first line of therapy if the appropriate device is available.
3 Current Treatment Options

3.1 Pulmonary Artery Stenosis

Figure 3.1: a) Balloon Dilation\(^1\) and b) Balloon dilation with stent\(^2\)

- Balloon Dilation: involves widening a narrowed vessel with a balloon dilation catheter (Figure 3.1). The vessel is generally over-dilated to achieve success. But in most cases the vessel eventually collapses back and has to be re-dilated. Hence, patients have to periodically undergo repeat dilations.

- Balloon dilation and stent placement: In order to circumvent the problems associated with balloon dilations, physicians now place bare metal stents in the vessel following balloon dilation to hold the vessel wall and prevent restenosis (Figure 3.1). Unfortunately, there are no pediatric stents available and hence physicians use size-matched adult stents where applicable. Although a viable substitution, this option can be used in only a handful of
patients currently. In very small infants stenting is not recommended as the difficulty and risks are very high. Additionally, stents that can expand to 18-20mm have to be used to accommodate the vessel's size as an adult. If the stent is not large enough, it will result in stenosis as the vessel grows requiring reintervention and stent replacement. Hence, in most infants balloon dilation is the preferred procedure.

- The cutting balloon: This procedure is similar to balloon dilation, but the balloon has tiny blades along it sides which are activated when the balloon gets dilated. The blades cut through the stenosed area, making it easier to dilate the vessel and create a larger opening.

- Surgery: Depending upon the level of stenosis and the complexity of surrounding vessels, various surgical methods can be employed.

3.2 Coarctation of Aorta
Surgery is the gold standard of treatment for CoA. One of two surgical options are employed for the repair of CoA

- In a procedure called end-to-end anastomosis, the surgeon removes the narrowed region of the aorta and joins the two ends of as shown in Figure 3.2(a).

- The subclavian artery is used to create a flap that will enlarge the aorta and alleviate the coarctation as shown is Figure 3.2(b).

In some cases balloon angioplasty in the catheterization lab can be used for the treatment of coarctation (Figure 3.2(c)). Although, surgery is the preferred method of treatment in infants, most patients will suffer from recurrent episodes
of CoA, which are normally treated with non-surgical balloon dilation or stent implantation.

Figure 3.2: CoA Repair (a) End-to-end anastomosis, (b) Subclavian artery flap, (c) Balloon Angioplasty
4 Clinical Background

The first pediatric stent implantations were successfully performed in 1989 by Dr. Charles Mullin using adult bare metal stents (BMS) in pediatric patients suffering from branch pulmonary artery stenosis or postoperative stenosis. Following the success of this procedure, pediatric stenting has been increasingly performed by physicians using off-label parts for the treatment of pulmonary artery stenosis, coarctation of aorta, patent ductus arteriosus and tetralogy of fallot.

Although stents are being increasingly used in pediatric patients, currently there are no stents available in the market specifically designed for pediatric patients. Hence, all stents used by pediatric cardiologists are “jury-rigged” adult stents. Adult bare metal stents used in pediatric patients pose some serious problems. Their rigid structure inhibits vessel growth and physicians have to periodically intervene to surgically remove the stent and redilate the vessel.

The role of a stent is temporary. A stent is required to support a healing artery for a limited period of time and prevent occlusion and negative remodeling after balloon dilation. Once the artery is healed, it is desirable for the stent to no longer be present so that endothelialization and arterial remodeling can occur and the artery can be restored to its natural flexibility. Permanent bare metal stents support the artery during its healing phase, but since they remain in the body after the artery has healed they do not allow the vessel wall to remodel and lead
to complications like in-stent thrombosis and restenosis over a period of time. In pediatrics, the problem is further compounded, as vessel growth is restrained by the presence of the stent requiring surgical removal of the device.

A pediatric bioabsorbable stent would not only circumvent all the issues associated with the use of adult devices in pediatric patients, but would also disappear after a pre-determined period of time circumventing the need for repeat interventions and allowing the growing vessel to develop naturally. This would preclude the requirement of repeat surgical interventions and allows the vessel to grow normally. Also, restenting is possible if required at a later stage.

Various bioabsorbable materials are being testing for the manufacture of bioabsorbable stents. Poly L lactic acid (PLLA) polymers have been extensively studied for over 50 years\textsuperscript{9,10} and have been used in medicine since 1966\textsuperscript{11,12} with a well documented safety and degradation profile. However PLLA stents have traditionally experienced poor biocompatibility, long degradation times (up to two years), inadequate resorption, insufficient mechanical strength and vessel wall inflammation.

The PediaStent prototype based on ART's technology uses a modified PLA composition which consists of a mix of D and L lactic acid (PDLLA) that affords several advantages over PLLA. Most importantly the PDLLA polymer provides greater control over structural degradation duration which can be tailored to
potentially be as brief as three months. Additionally, the composition of the polymer ensures that little to no traceable residue is left behind, virtually eliminating inflammation of the blood vessel wall. The polymer's design also balances biocompatibility, biomechanics and bioresorption without affecting healing. Preclinical studies conducted by ART have demonstrated that the ART stent exhibits excellent biocompatibility and biomechanics without the need of preventive drugs. Data from ART's preclinical studies can be leveraged for PediaStent development and are outlined below.

Classically stent recoil has been an issue with bioabsorbable stents due to loss of mechanical properties after deployment. Recoil has also been observed due to stent strut fractures during crimping and deployment. In order to circumvent these issues, ART has developed a proprietary molding process and a proprietary memory shaping process that ensures that the biomechanical properties of the adult stent the molecular weight of the stent at >85% of its initial weight from granules to sterilization\textsuperscript{13}. As shown in Error! Reference source not found., the PLA stent has a learning process resulting in a slight 5% diameter increase one hour after deployment and 10% after two hours.
The diameter does not change much after that and there is no recoil observed at seven days. Figure 4.2 shows that stent crimping or deployment does not result in strut cracks or crazing.

Figure 4.2: A) A PLA stent crimped on a balloon shows no cracks or crazing. B) A fully deployed PLA stent without any strut cracks or crazing

In vitro studies in 0.13M PBS at 37°C and in vivo studies in rabbits to evaluate hydration and percent change in molecular weight (Y-axis in Error! Reference source not found.) changes during bioresorption show that the in vitro model and the in vivo model have the same resorption profile.

Figure 4.3: Resorption profile of stereo copolymers a) in vitro and b) in vivo.
Biocompatibility studies were conducted by implanting the stents in rabbit iliac arteries and evaluating at one, four and six months.

Complete endothelialization was observed at one month by CD31 immunostaining (Error! Reference source not found.)\textsuperscript{13}. RAM11 immunostaining (Figure 4.5) showed almost no macrophage infiltration at one, four and six months indicating little to no inflammation during bioresorption\textsuperscript{13}

Histological analysis (Error! Reference source not found.) demonstrated that even at peak PLA resorption there was no inflammation or smooth muscle cell proliferation demonstrating that there is no hyperplasia at six months \textsuperscript{13}
Angiographic studies at six months (Error! Reference source not found.) demonstrated that there was no endothelial dysfunction despite PLA resorption\textsuperscript{13}

ART has conducted preclinical studies in 48 porcine arteries and have shown that

- biodegradation of their stent is measurable and begins at the day of implant
- the stent retains high radial strength and hence maintains structural integrity during biodegradation
- stent resorption causes virtually no vessel wall inflammation
5 Lactic Acid Biochemistry

All nutrients in the body are finally converted to glucose which is further broken down to provide energy to the body. Glucose, the most common simple carbohydrate formed in the body is systematically broken down via glycolysis to a three carbon unit. One molecule of glucose is broken down to two molecules of pyruvate via glycolysis in the cytoplasm of the cell. During this process two molecules of ATP and two molecules of NADH are generated. NADH stores energy in the form of electrons in an O2 environment. The NADH is transported to the mitochondria where it is oxidized via oxidative phosphorylation to generate NAD+ and ATP. The NAD+ is then recycled to the cytoplasm to undergo another round of reduction-oxidation (redox) reaction.

Under aerobic conditions, pyruvate generated through glycolysis enters the Kreb’s cycle in the mitochondria and is further degraded to CO₂ and H₂O to generate energy in the form of ATP and NADH. NADH undergoes oxidative phosphorylation to generate ATP which is utilized by the body for various activities.
Figure 5.1: Lactic Acid Metabolism

Under anaerobic conditions, for example in the muscle during periods of extreme physical activity, pyruvate formed by glycolysis is converted to lactate instead of entering the Kreb’s cycle. This is because in the absence of oxygen, there is a paucity of NAD+. Conversion of pyruvate to lactate regenerates NAD+ which is recycled into the glycolytic pathway to continue the cycle and generate ATP. Lactic acid produced in the muscle during this process is converted back to pyruvate when sufficient oxygen is available, which can enter the Kreb’s cycle and degraded to CO₂ and H₂O.
6 Poly-lactide polymers

6.1 Historical Experience and Applications
Lactide – based polymers have been the most extensively studied polymers as they are known to be biocompatible and their biodegradability profile and mechanical properties can be easily modified. Lactide – based polymers have been in use for over 35 years\(^\text{14}\) in other clinical items like biodegradable sutures\(^\text{14}\), soft tissue implants, orthopedic implants like screws and plates\(^\text{14}\), drug delivery as well as cardiovascular applications\(^\text{15}\). Hence, its safety and degradation profile is well documented.

Igaki and Tamai (Igaki Medical Planning Co, Ltd) were the first to successfully develop and implant a PLLA stent in humans\(^\text{16}\). Following the success of the Igaki – Tamai stent Abbott Vascular introduced the Poly-L lactic acid (PLLA) everolimus – eluting stent, and reported positive outcomes of its ABSORB clinical trial at 3-year follow-up in 2009\(^\text{17}\). Abbott started enrolling patients for its ABSORB EXTEND phase II trial in Jan 2010 to study safety and efficacy of the stent in 1000 patients. This trial is estimated to be completed in 2015. Abbott announced on Jan 10\(^\text{th}\) 2011, that they have received CE Mark approval for the world’s first coronary bioabsorbable stent. They plan to make the sents available in European markets by the end of 2012\(^\text{18}\).

However there are some problems associated with the current PLLA stents like poor biocompatibility, long degradation times (up to 2 years), inadequate
degradation and resorption, insufficient mechanical strength, inflammatory
degradation products that result in blood vessel wall inflammation and
inadequate drug release when used as a drug delivery system.

6.2 Degradation
The most important feature of PLLA is that it provides a temporary scaffold in vivo and then gradually degrades without leaving any toxic residues in the body. PLLA is metabolized into carbon dioxide and water via the Krebs cycle (Figure 6.2). There are five major stages of PLLA degradation

- Hydration: The polymer absorbs water from the surrounding tissue after the implant is placed in the body (Error! Reference source not found.). The rate of hydration is dependent on the polymer composition, molecular weight, size and shape of the implant, and position in the body
- Depolymerization of the polymer backbone: The water absorbed by the polymer will reach with the covalent bonds and cleave the polymer chain into smaller chains, thereby decreasing the molecular weight of the polymer (Error! Reference source not found.).

![Figure 6.1: Hydrolysis and depolymerization of PLLA](image)

Figure 6.1: Hydrolysis and depolymerization of PLLA
• Loss of Mass and Integrity: As the polymer backbone continues to depolymerize, the polymer begins to lose its cohesive strength and starts breaking up into smaller pieces.

• Absorption: At this point the smaller fragments continue hydrolyzing to yield monomeric lactic acid subunits which are absorbed into the intracellular fluid. Alternatively, the smaller fragments might get phagocytosed by macrophages and get assimilated.

• Elimination: The lactic acid monomers are converted to pyruvate which enters the Kreb’s cycle to yield H₂O and CO₂

![Figure 6.2: PLLA degradation profile](image)

6.3 Factors Affecting the Rate of Degradation

6.3.1 Polymer Length

Longer the polymer chain length, higher the molecular weight of the implant. The higher molecular weight polymer will take longer to absorb the water and degrade.
6.3.2 Hydrophilicity

Highly hydrophilic molecules will absorb more water and at a faster rate resulting in faster cleavage of the polymer backbone. The presence of the -CH3 group makes the lactide polymer more hydrophobic and sterically less accessible to water molecules.

6.3.3 Crystallinity

A crystalline polymer degrades much slower than an amorphous polymer. PLLA polymer is crystalline whereas a copolymer of L and D lactic acid is amorphous. Altering the ratio of L and D lactic acids in the polymer affects the crystallinity of the polymer which influences the degradation time of the polymer. A PLLA polymer degrades much slower than a Poly D, L lactic acid polymer. Since the Abbott ABSORB stent and the Igaki Tamai stent are made of PLLA their degradation time is greater than 2 years. Since ART stent is a D, L lactic acid stereocopolymer, the degradation time can be controlled by altering the ratio of D and L lactic acid polymers. A stent made of PLA_{92} polymer degrades slower than a stent made of PLA_{50} polymer when implanted into rabbit aortas^{20}.

Overall lactide-based polymers are a very promising class of materials for the development of bioabsorbable stents. These molecules have been in use in medicine for over 50 years and have a known biomechanical and bioabsorption profile with non-toxic, easily assimilated end products. With the right combination of stereo-polymers and design that can maintain biomechanical integrity and
strength to provide support to the vessel walls without strut cracks or crazing, it
could change the paradigm of cardiovascular treatment in the coming years.
7 Addressable Market Size

In pediatric patients, the major indications for stenting are pulmonary artery stenosis and coarctation of the aorta. These are congenital disorders that affect a very small patient population but are a very important unmet market need. Every year 36,000 children in the US are born with a congenital heart disease. An internal survey conducted of 30 pediatric cardiologists and interventional cardiologists in the US indicated that stent is one of the largest unmet market need in pediatrics. Due to the lack of appropriate available treatment options physicians are compelled to either "jury-rig" adult devices for pediatric applications or defer treatment till the patient is old enough for the devices available on the market. Both practices cause considerable discomfort and malaise to the sick infant. In the absence of available devices, surgical intervention is the treatment of choice for many indications.

According to the agency for Healthcare Research and Policy (AHRQ), in the US an average of 2,200 patients (6% of all CHDs) presented with coarctation of aorta and 1,650 patients (4.6% of all CHDs) presented with pulmonary artery stenosis as the principal indication in 2008. Pulmonary artery stenosis is also associated with various other defects like Tetralogy of Fallot, ventricular septal defect, atrial septal defect and patent ductus arteriosus. According to the AHRQ over 17,000 children were treated for pulmonary stenosis associated with all indications in 2006. A study conducted at the University of Arkansas for Medical Sciences regarding the long term outcomes of pulmonary artery stenting found
that over a 10 year follow-up period, 49% of stents required reintervention due to
enlargement of the vessel as the child get older and/or in stent thrombosis\textsuperscript{5}.
Depending upon the age of the patient, the device used and the disease state
one or several repeat interventions maybe required.

Stenting has been successfully accomplished using adult bare metal stents in
pediatric patients for pulmonary artery stenosis as an isolated procedure\textsuperscript{21} or in
association with Patent Ductus Arteriosus\textsuperscript{22} or Tetralogy of Fallot\textsuperscript{8}. But the
numbers of procedures being currently performed are relatively few due to the
unavailability of the right stents and the complications associated with BMS.

In a personal communication with Dr. Tom Forbes, Director of cardiac
catheterization lab at Children’s Hospital of Michigan and Dr. Larry Latson,
Medical Director of the cardiac catheterization laboratory in the Center for
pediatric and congenital heart diseases at the Cleveland Clinic indicated that at
least 70% of all angioplasty patients would be candidates for stenting. According
to the AHRQ there were nearly 2500 angioplasty procedures on non-coronary
vessels in pediatric patients in 2006 of which 1700 patients would be candidates
for stenting. Dr. Latson indicated that he transplants at least two stents in each
patient which is nearly 3500 stents.

In a personal communication, Dr. Tom Forbes, indicated that the current standard
of treatment for coarctation of aorta is surgery and hence testing stents for this
indication will open up an entire new market. There are nearly 2200 patients presenting with CoA every year.

Hence the US market for bioresorbable pediatric stents for CHD is at least 5700. PediaStent also plans to market the stents internationally. Since ART has a presence in Europe, they would enter these markets first followed by the Asia – Pacific.

Following the success of the stents in CHDs, PediaStent plans to develop urethral and pulmonary stents for pediatrics. Currently, bare metal stents are in use for these indications.
8 Competition

The first pediatric stent was implanted in 1989 by Dr. Charles Mullin. It has been over 20 years since the first implantation yet there are still no stents specifically designed for pediatric patients available in the market. Pediatric cardiologists adapt adult bare metal stents for pediatric implantations. The most commonly used balloon expandable bare metal stents in pediatrics are outlined in Table 8.1

Table 8.1: Bare metal stents used in pediatrics

<table>
<thead>
<tr>
<th>Company</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordis</td>
<td>Palmaz Genesis, Palmaz XD and Palmaz XL, Bx Velocity, Aviator SDS</td>
</tr>
<tr>
<td>Medtronic</td>
<td>Driver Stent</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Liberte Stent</td>
</tr>
<tr>
<td>Ev3</td>
<td>Intrastent Doublestrut LD stent, Intrastent Mega LD stent and Intrastent Max LD stent</td>
</tr>
<tr>
<td>NuMed</td>
<td>Cheatham-Platinum (CP) six-zig stent, CP eight-zig stent</td>
</tr>
</tbody>
</table>

Currently there are no bioabsorbable stents available on the market but various companies are in clinical and pre-clinical trials for the development of these stents for the adult market.

Phase II ABSORB clinical trials conducted with Abbott Vascular’s BVS stent in US has yielded very promising data and is farthest along in the developmental
stage. Abbott is currently enrolling patients in the ABSORB EXTEND trial which intends to enroll 1000 patients in order to continue assessing the safety and efficacy of the BVS stent. The estimated completion date of this trial is 2015. Abbott obtained CE Mark approval in Jan 2011 and intends to start marketing the stent in Europe towards the latter half of 2010.

Kyoto Medical's Igaki Tamai stent has obtained CE Mark for use of the stent in peripheral artery and efforts are underway to obtain approval for the coronary artery as well.

Table 8.2 lists all the companies that are currently involved in developing bioabsorbable stents for the adult market.
<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Material</th>
<th>Design</th>
<th>Development Stage</th>
<th>Performance</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott Vascular</td>
<td>Bioabsorbable Everolimus Euting</td>
<td>Polymer of Poly L lactic acid</td>
<td>Circumferential hoops of PLLA with 150uM struts joined by straight bridges</td>
<td>ABSORB Phase II clinical trials completed (2 year follow-up data available)</td>
<td>Proven safe, low rate of MACE (4.4%), low inflammation, no thromboses, low in-stent rate of late loss of 0.19mm</td>
<td>ABSORB Extend trial with 1000 patients currently recruiting. CE Mark obtained in Jan 2011</td>
</tr>
<tr>
<td>Arterial Remodeling Technologies (ART)</td>
<td>Bioabsorbable stent (ART stent)</td>
<td>Specific ratio of D and L Poly-lactide units</td>
<td>Mesh configuration</td>
<td>Pre-clinical studies</td>
<td>No inflammation, retains structural integrity during degradation, mechanical scaffold lost in 3 mos, and</td>
<td>Pre-clinical studies completed. Clinical trials in early 2012</td>
</tr>
<tr>
<td>Company</td>
<td>Model</td>
<td>Material/Design</td>
<td>Approval Status</td>
<td>Benefits</td>
<td>Trials Outcome</td>
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<tr>
<td>Kyoto Medical</td>
<td>Igaki Tamai Coronary Stent</td>
<td>Poly L Lactic Acid, a zigzag helical coil design</td>
<td>CE Mark in 2007 for peripheral artery stent. Phase I coronary trial completed</td>
<td>Complete resorption in 18 mos, Low thrombosis, no vascularization, arterial remodeling at stented site</td>
<td>Clinical trials</td>
<td></td>
</tr>
<tr>
<td>Reva Medical Inc</td>
<td>ReZolve bioresorbable drug-eluting stent</td>
<td>Tyrosine-derived polycarbonate polymer, patented slide and lock design minimizes polymer thickness and material strength</td>
<td>Phase I clinical trials completed</td>
<td>Unfavorable revascularization rate at 4-6 months due to reduced stent diameter</td>
<td>Clinical trials</td>
<td></td>
</tr>
<tr>
<td>Bio-absorbable Therapeutics</td>
<td>DTI Sirolimus – eluting stent</td>
<td>Salicylic acid polymer, tube with laser cut voids.</td>
<td>Pre-Clinical</td>
<td>High neointimal hyperplasia</td>
<td>Stent redesign with thinner</td>
<td></td>
</tr>
<tr>
<td>Company</td>
<td>Description</td>
<td>Characteristics</td>
<td>Phase</td>
<td>Results</td>
<td>Status</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>-------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>OrbusNeich</td>
<td>Genous bioengineered stents</td>
<td>R stent with Poly-lactide multipolymer coated with hCD34 antibody</td>
<td>Phase II</td>
<td>Comparative or better performance than Taxus Liberte at 2 year followup</td>
<td>Recruiting for Phase II trial completed</td>
<td></td>
</tr>
<tr>
<td>Elixir Medical</td>
<td>BDES</td>
<td>PLLA polymer coated with Novolimus or Myolimus</td>
<td>Preclinical</td>
<td>Mechanical properties and delivery system performance similar to metal stents</td>
<td>Preclinical studies ongoing in porcine model</td>
<td></td>
</tr>
</tbody>
</table>
Analysis of Porter’s five forces shows that PediaStent would be well placed in the competitive market upon entry. Since most companies are focused on developing stents for the adult market, PediaStent would face very little competition in the niche pediatric segment. Being the only product on the market would reduce buyer power allowing PediaStent to price the product at a premium. With a highly specialized product, they would not have to worry about threat of substitution.
However, since so many companies are developing products for the adult market, the threat of new entrants is very high. Due to the small market size, the threat of competitive rivalry for market share and dominance would also increase if there was more than one player in the market. Consequently, the first to market will have an obvious advantage if the product is superior. Since, PediaWorks intends to outsource most of its manufacturing, and the requirements are specialized, suppliers would have some increased bargaining power.

In summary, if PediaWorks can be first to market, and establish brand loyalty and confidence, it would capture a high market share allowing it to negotiate competitive threats.
10 Intellectual Property Protection

PediaWorks’ stent has been developed by research conducted by Drs. Antoine Lafont and Michael Vert at the Cleveland Clinic and the Centre National de Recherche Scientifique (CNRS) and is protected by intellectual property originated from the Cleveland Clinic, C.N.R.S., and the Necker University, Paris. PediaWorks is developing the pediatric stent in collaboration with Arterial Remodelling Technologies (ART) which has licensed exclusive rights to the technology from these institutions. Once they have finalized the terms of the agreement, they plan to license the technology from ART for pediatric applications.

10.1 Product Development
PediaWorks is working in collaboration with ART and they have leveraged their tooling and manufacturing capabilities for stent design to design prototypes of pediatric stents. Pediatric stents will be implanted in larger vessels and must have a larger diameter than the adult coronary stents that ART has designed and tested till date. They paid ART to create the appropriate tooling and design stents according to their specifications outlined in Table 10.1. The expanded and crimped prototypes are shown in Error! Reference source not found.
### Table 10.1: Pediatric stent specifications provided to ART

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Specification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length</td>
<td>12mm-16mm</td>
</tr>
<tr>
<td>Diameter (final)</td>
<td>5mm-10mm</td>
</tr>
<tr>
<td>Thickness</td>
<td>Stent adds only 1Fr to 4Fr balloon (introduction)</td>
</tr>
<tr>
<td>Flexibility</td>
<td>Greater flexibility for vessel conformity and stent tractability over a wire</td>
</tr>
<tr>
<td>Absorbability</td>
<td>6-9 months for loss of mechanical structure</td>
</tr>
<tr>
<td>Radial Strength</td>
<td>5.6 psi - 6.2 psi</td>
</tr>
</tbody>
</table>

ART’s engineers have successfully designed ten prototype stents for PediaStent (
Table 10.2) and performed the necessary biomechanical tests on them to test for mechanical strength, chemical performance and radial performance. As can be seen in
Table 10.2, the stents were designed as per their recommendations and performed well on biomechanical testing.

Figure 10.1: a) Prototype and b) Prototype crimped
Table 10.2: Biomechanical testing results of pediatric stents

<table>
<thead>
<tr>
<th></th>
<th>CUTTING STENT (inspection 3 samples)</th>
<th>CRIMPED STENT</th>
<th>EXPANDED STENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight loss</td>
<td>15%</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>compared to raw material</td>
<td></td>
<td></td>
<td>Chemical Inspection</td>
</tr>
<tr>
<td>Stiffness</td>
<td>825 N/mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial Force</td>
<td>33N</td>
<td></td>
<td>Mechanical Inspection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRIMPED STENT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent profile on a 7mm</td>
<td>2.15mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diameter balloon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXPANDED STENT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimensions (average of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 samples)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of expanded</td>
<td>7.81mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stent on balloon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(inflation pressure: 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bars)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of expanded</td>
<td>7.56mm (-3.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stent after balloon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deflation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diameter of expanded</td>
<td>7.34mm (-6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stent after 120min in</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a 37°C bath</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of expanded</td>
<td>14.9mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>stent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Inspection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial force</td>
<td>34N</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiffness</td>
<td>821 N/mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
11 Preclinical and clinical studies

Following prototype development and mechanical testing, the next step will be to test the device in animal models. ART has tested the device in rabbits and porcine and has very promising data. Since in a pediatric patient, the vessels are still growing PediaStent plans to test the stent in juvenile pigs whose vessels are growing at rates similar to those observed in humans.

The FDA has established a pediatric bioabsorbable stent task force to lay down appropriate guidelines for preclinical and clinical testing of these devices. PediaWorks is a part of this task force and they participate in regular calls with the FDA, clinicians and companies to determine the best possible clinical design for pediatric bioabsorbable stent assessment. Based on discussions and suggestions obtained during calls on preclinical testing they have established that Pulmonary Artery Stenosis (PAS) would be the best indication to initially test these stents.

Advantages of using PAS as a stenting models are

- In a porcine model with PAS it is possible to stent a contralateral vessel in the same animal with a BMS as a control.
- It would be feasible to determine downstream effects of the stent’s degradation products by check for embolization in the lungs.

Based on these recommendations as well as discussions with Drs. Tom Forbes and Larry Latson, PediaStent has developed a pre-clinical trial design.
11.1 Preclinical Trial Study Design
Sixteen juvenile pulmonary artery stenotic pigs weighing 15 -25 Kg will be stented at one or more of the following sites – main pulmonary artery (MPA), left pulmonary artery (LPA), right pulmonary artery (RPA), aorta and Superior Vena Cava (SVC). Bare metal stents will be implanted in the same animals as controls. Four animals each will be sacrificed at one month, three months, six months and one year. Each animal will be recatheterized before sacrifice. At each time point, stents will be evaluated for strut fractures and embolization via MRI/CT of the head or lower lung lobe segments prior to explantation. *In vivo* and *ex vivo* hoop stent will be measured at three months and six months to assess radial strength and structural integrity of the stents. Local inflammatory response will be assessed at each time point by histopathological evaluation of the vessels. As strongly suggested by the FDA, this study will be conducted in a GLP facility to assure the highest fidelity.

11.1.1 *Project Schedule for preclinical studies*

PediaStent expects to complete the pre-clinical studies in one year. Table 11.1 outlines the proposed schedule of the clinical trial design.
Table 11.1: Proposed schedule for preclinical studies

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent manufacture and crimping</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent explanted at 1 month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent explanted at 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent explanted at 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent explanted at 12 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11.2 Clinical Studies
Following the successful completion of pre-clinical studies which will establish safety of the stent in porcine models, PediaStent intends to initiate clinical studies to confirm safety in humans. Clinical trials need not be randomized or controlled since the patient size is so small. There are no set guidelines available that specify the data required to demonstrate efficacy, but the FDA encourages companies to work with them to establish appropriate guidelines for the trial.

Medtronic submitted the HDE for the Melody Transcatheter Pulmonary Valve with data from 30 patients that had been monitored for a period of 6 months. They also included data from a UK study which included 68 patients. Based on the above, FDA granted Medtronic permission to market the device as a Humanitarian Use Device (HUD) to be used in institutions that have an IRB approval.
Based on discussions with a regulatory consultant, PediaStent has determined that a clinical trial testing the device in 30-50 patients monitored for a period of one year would be adequate to file for an HDE.

Since Drs Forbes and Latson will be involved with the pre-clinical studies, it would be optimum to have them involved in the clinical trials as well. If they agree to participate in the clinical studies as well, PediaStent can conduct trials at the Children’s Hospital of Michigan and the Cleveland Clinic Foundation. Dr. Tom Forbes, Director of Cardiac Catheterization lab at Children’s Hospital of Michigan indicated that they performed 35 angioplasty procedures of the pulmonary artery in 2010 and 25 of these were primary stenting procedures. It is anticipated that it would take a year to complete patient recruitment and another year of follow-up to confirm the safety and probable efficacy of the stents. After this data is obtained, they will file for an HDE which should be approved in 75 days. Once they obtain FDA approval they will gear up production to enter the market. Table 11.2 lists the milestones and timelines of these milestones.
### Table 11.2: Milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Start</th>
<th>End</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prototype Development and Mechanical Testing</td>
<td>Jan 2012</td>
<td>Feb 2012</td>
</tr>
<tr>
<td>Preclinical Trials</td>
<td>June 2012</td>
<td>June 2013</td>
</tr>
<tr>
<td>Clinical Trial</td>
<td>Jan 2013</td>
<td>Dec 2015</td>
</tr>
<tr>
<td>HDE application</td>
<td>Jan 2016</td>
<td></td>
</tr>
<tr>
<td>FDA Approval</td>
<td>March 2016</td>
<td></td>
</tr>
<tr>
<td>Market Entry</td>
<td>June 2016</td>
<td></td>
</tr>
</tbody>
</table>
### 12 Pricing

Table 12.1: Total cost for developing PediaStent

<table>
<thead>
<tr>
<th>Materials and Methods</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prototype Development</td>
<td>$70,000</td>
</tr>
<tr>
<td>Preclinical Trials</td>
<td>$250,000</td>
</tr>
<tr>
<td>IRB fees</td>
<td>$50,800</td>
</tr>
<tr>
<td>Clinical Trials</td>
<td>$502,350</td>
</tr>
<tr>
<td>MRI followup (every 3 months for 1 year)</td>
<td>$720,000</td>
</tr>
<tr>
<td>Total Materials and Methods</td>
<td>$1,593,150</td>
</tr>
<tr>
<td>Staffing and Payroll (for 5 years)</td>
<td>$3,365,840</td>
</tr>
<tr>
<td>Total</td>
<td>$4,958,990</td>
</tr>
</tbody>
</table>

Table 12.1 outlines the total costs of materials and labor for the development of PediaStent over a period of five years. For prototype development, I have assumed an approximate cost of $1000 per stent based on the information that PediaWorks paid ART $7000 for the manufacture of the first 10 prototypes. These were provided to them as fully expanded stents which would have to be crimped and balloon mounted for an additional charge.

Based on a quote obtained from a Clinical Research Organization (CRO), the cost of conducting pre-clinical studies were determined to be at least $250,000 if the studies were conducted in a Good Laboratory Practices (GLP) – certified facility.
Conversations with regulatory experts have indicated that due to increased regulations by the FDA it was strongly advisable to conduct the pre-clinical studies in a GLP facility.

Table 12.2: IRB fees and cost

<table>
<thead>
<tr>
<th>One time IRB fee per institution</th>
<th>Fees</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRB review Fee</td>
<td>$2,250</td>
</tr>
<tr>
<td>IRB continuing review fee</td>
<td>$750</td>
</tr>
<tr>
<td>IRB Amendment review</td>
<td>$500</td>
</tr>
<tr>
<td>IRB preparation Fee</td>
<td>$1,500</td>
</tr>
<tr>
<td>Administrative Fee</td>
<td>$3,000</td>
</tr>
<tr>
<td>Total one time institutional fees</td>
<td>$8,000</td>
</tr>
</tbody>
</table>

Five institutions: $40,000

Continuing fees

Document storage fee ($100/year for 2 years): $10,000
Source document binders ($8 per patient per year for 2 years): $800
Total IRB fees: $50,800

Since this product will be tested as a Humanitarian Use Device, an Institutional Review Board (IRB) application will have to be filed at each institution where the trial is conducted. Assuming that the trial will be conducted at five institutions enrolling a total of 50 patients,

Table 12.2 outlines the total IRB fees and cost that the clinical trials will incur.
Assuming that each stent and angioplasty device and procedure cost would be $8658 per procedure\textsuperscript{23} and physician’s fees per procedure would be $1389\textsuperscript{24}, the total procedure cost for 50 patients would be $502,350.

After the procedure each patient will have to be followed up on an ongoing basis to monitor safety of the device implantation to check for stent migration, stent breakage or downstream embolization due to stent breakage. Patients will be monitored via MRI every 3 months for the first year. The average cost of an MRI in the Cleveland region is $3600. Using this as the cost of followup for each visit, the total cost of followup over 50 patients will be $720,000.

As the project progresses, PediaWorks will have to increasingly hire more people to manage the clinical, engineering and marketing needs of the organization.
Table 12.3 illustrates the potential staffing and salary requirements of PediaWorks from year one to year five as the company develops the product.
Based on these calculations, PediaWorks will incur costs of $5 million over a period of five years for the development of PediaStent.

Table 12.3: PediaStent staffing organization

<table>
<thead>
<tr>
<th>Position</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEO</td>
<td>$125,000</td>
<td>$256,250</td>
<td>$269,063</td>
<td>$282,516</td>
<td>$296,641</td>
</tr>
<tr>
<td>Study Manager</td>
<td>$75,000</td>
<td>$78,750</td>
<td>$82,688</td>
<td>$86,822</td>
<td></td>
</tr>
<tr>
<td>Q/A Manager</td>
<td>$85,000</td>
<td>$89,250</td>
<td>$93,713</td>
<td>$98,398</td>
<td></td>
</tr>
<tr>
<td>COO</td>
<td></td>
<td>$185,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VP Sales &amp; Marketing</td>
<td></td>
<td>$150,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marketing Analyst</td>
<td></td>
<td>$50,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VP Engineering</td>
<td></td>
<td>$150,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Field Support Manager</td>
<td></td>
<td></td>
<td>$90,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical/Field Support</td>
<td></td>
<td></td>
<td>$65,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical/Field Support</td>
<td></td>
<td></td>
<td>$65,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engineer</td>
<td></td>
<td></td>
<td>$70,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office manager/bookkeeper</td>
<td></td>
<td></td>
<td>$60,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total Payroll</strong></td>
<td>$200,000</td>
<td>$420,000</td>
<td>$441,000</td>
<td>$998,050</td>
<td>$1,306,790</td>
</tr>
<tr>
<td><strong>Average Payroll</strong></td>
<td>$100,000</td>
<td>$140,000</td>
<td>$147,000</td>
<td>$142,579</td>
<td>$118,799</td>
</tr>
</tbody>
</table>
12.1 Price Justification
Using the formula suggested by Dr. Galanaud\textsuperscript{23} to calculate the breakeven point of drug-eluting stents over bare metal stents, the breakeven point of bioabsorbable stent over bare metal stent will be calculated as follows

\[
\text{Price of bioabsorbable stent} = \text{price of BMS} + \text{avoided revascularization rate}(0.5 \times \text{cost of surgery} + 0.5 \times \text{cost of balloon angioplasty})/2
\]

I will be using Coarctation of Aorta as an indication to illustrate this calculation. Approximately 17\% of patients below the age of 6 months, who undergo repair of native CoA via surgery, suffer from repeat CoA and have to undergo a secondary procedure which is either surgery or balloon angioplasty.\textsuperscript{25} Assuming that a patient receiving PediaStent will not have to undergo repeat revascularization, the avoided rate of revascularization with stenting is 17\%. According to a study published by Dr. Fruh S, 50\% of patients with repeat CoA will undergo a surgical repair and the remaining 50\% will undergo balloon angioplasty\textsuperscript{25} which is factored in the equation. Dr. Latson at the Cleveland Clinic indicated that he typically puts an average of 2 stents per procedure which is reflected in the denominator. The average price of a BMS in the US is $1500\textsuperscript{23}.

The average cost of surgery is approximately $12,500 and the average cost of balloon angioplasty is approximately $5,300\textsuperscript{26}. Incorporating these numbers in the above equation, the breakeven price of a bioabsorbable stent is $2500.
As shown in Table 12.4, if PediaWorks prices the stent at $2,500, it would take them over 7 years to recover the cost of developing the product while incurring additional costs of manufacturing, salary and SG&A. At this price it would be several years before PediaWorks could become cash positive and may not be able to survive for so long without cash flow. PediaWorks plans to price the stent at $5,000. At this price, it will recover development costs by 6 years and can then move on towards becoming cash positive. According to FDA’s guidelines for HDE,
since the market size of HDE products is so small, products can be priced at a premium to help recover development costs.

13 FDA approval

PediaWorks plans to apply for “Humanitarian Device Exemption” (HDE) with the FDA to market the device as a “Humanitarian Use Device” (HUD). A HDE application is similar to a Pre-Market Approval (PMA) application except that a PMA requires the demonstration of safety and efficacy whereas the HDE is exempt from the requirement of efficacy. Table 13.1 compares HDE and PMA approval requirements.

Table 13.1: Comparision of HDE and PMA\textsuperscript{27}

<table>
<thead>
<tr>
<th></th>
<th>HDE</th>
<th>PMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval criteria</td>
<td>Safety (probable efficacy)</td>
<td>Safety and efficacy</td>
</tr>
<tr>
<td>Patient population</td>
<td>&gt;4000</td>
<td>Any</td>
</tr>
<tr>
<td>Study Design</td>
<td>Clinical data preferable but not necessary</td>
<td>Requires randomized controlled trials</td>
</tr>
<tr>
<td>IRB approval required to market</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Selling Price</td>
<td>Commensurate with cost of development</td>
<td>Commensurate with market</td>
</tr>
<tr>
<td>Time to review by FDA</td>
<td>75 days</td>
<td>180 days</td>
</tr>
</tbody>
</table>
The application must provide information that attests that the device “does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use.” A HUD is defined by the FDA as a “medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.” This exemption was put in place to incentivize industries to develop treatments affecting small patient populations.

In order to market the device as HUD, the device must be appropriately labeled to state that the device is for Humanitarian Use Only and although approved by the FDA, the efficacy of the device for the particular indication has not been established. Additionally, the device can only be used in facilities that have an Institutional Review Board (IRB) in place to monitor the clinical testing of the device. The device can be marketed as an HUD only if there are less than 4000 patients per indication being treated with the device annually.

Since companies are not required to demonstrate efficacy for HUD, they can conduct shorter clinical studies on a smaller population of patients in order to obtain approval. Hence, the stents can reach the deserving patient population in a shorter period of time. Under IRB supervision, they will continue to collect data in patients who do get the stents implanted to demonstrate the efficacy of the device for that particular indication.
The FDA has approved 50 devices under HDE till date and approximately 20% of these approvals are for pediatric devices.

Table 13.2 lists the pediatric devices that have been approved under HDE for the treatment of cardiac congenital heart diseases.

Table 13.2: Pediatric devices approved as HUD

<table>
<thead>
<tr>
<th>Product</th>
<th>Manufacturer</th>
<th>Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melody Transcatheter Pulmonary Valve</td>
<td>Medtronic</td>
<td>Jan 2010</td>
</tr>
<tr>
<td>DeBakey VAD Child Left Ventricular Assist System</td>
<td>MicroMed Technology, Inc.</td>
<td>Feb 2004</td>
</tr>
<tr>
<td>Contegra pulmonary valve</td>
<td>Medtronic</td>
<td>Nov 2003</td>
</tr>
<tr>
<td>Amplatzer PFO Occluder</td>
<td>AGA Medical</td>
<td>April 2002</td>
</tr>
<tr>
<td>CardioSEAL Septal Occlusion System</td>
<td>Nitinol Medical Technologies, Inc.</td>
<td>Sept 1999</td>
</tr>
<tr>
<td>Shelhigh Pulmonic Valve Conduit Model NR-4000 with &quot;No-React®&quot; Treatment</td>
<td>Shelhigh, Inc.</td>
<td>Sept 1999</td>
</tr>
</tbody>
</table>
14 Reimbursement

Healthcare costs are paid by

1. Private Insurance Companies: like Blue Cross Blue Shield, Anthem, Aetna, Cigna, Wellpoint and HMO’s like Kaiser Permanente provide insurance at a premium paid by employers or individuals.

2. Centers for Medicare and Medicaid Services (CMS): Medicare and Medicaid are the federal insurance agencies. Medicare covers patients who are 65 years or older, disabled and those suffering from end-stage renal disease. Medicaid is a state-administered assistance program that covers people who are at or below the poverty level. Reimbursement and eligibility varies from state to state.

3. Patient (out-of-pocket): Patients who do not have insurance can choose to pay out-of-pocket, but this could change based on the healthcare reform proposed by the government under which every person will be required to have health insurance.

Medicare and Medicaid play a pivotal role in deciding the payment structure and amounts. Most private payers will have their own structure and system for reimbursement, but government reimbursement policies and payments influence private payer payments as they’ll. The three components that must be in place for reimbursement are

- Coverage
- Coding
- Payment
14.1 Coverage

14.1.1 Centers for Medicare and Medicaid Services

Medicare covers products based on the criteria of "reasonable and necessary" for the diagnosis or treatment of the patient. Medicare evaluates evidence to determine if the product improves health outcomes and if it is applicable to the Medicare population. Coverage can be obtained through one of the following three routes:

14.1.1.1 Existing payment categories and codes

If a similar device or procedure is already available that is being covered by Medicare, the new device can be billed using existing codes.

14.1.1.2 Local Coverage

Manufacturers have to work with Medicare workers in each specific region to negotiate appropriate coverage.

14.1.1.3 National Coverage

If the medical device has significant advantages over existing treatments, Medicare will implement a national coverage decision.

14.1.2 Private payers

Insurance companies may include an economic analysis by conducting a "Technology Assessment review" which uses the following criteria for assessment according to Blue Cross and Blue Shield.
• The device is FDA approved
• Adequate scientific evidence is available
• Technology improves health outcomes
• Technology is at least as beneficial as existing technologies
• Improvements are observed outside of the investigational setting

Private payers generally tend to follow CMS in making coverage decisions. 95% of devices do not go through a technology assessment review.

14.2 Coding
Codes are used on reimbursement forms to define the products and services used and the diseases or diagnoses they were used for.

• Procedures are products are identified by CPT, HCPCS or ICD-9 procedure codes
• Diagnosis and diseases are identified by ICD-9 codes

14.2.1 Current Procedural Terminology Codes (CPT)
CPT codes are defined by the American Medical Association (AMA) and are used to identify services provided by the physician. Medicare also publishes the CPT codes as HCPCS (Healthcare Common Procedure Coding System) Level I. Products and services not identified by HCPCS I are covered in HCPCS II
14.2.2 The International Classification of Diseases, Ninth Edition (ICD-9)

ICD-9 is managed by the American Hospital Association (AHA) in the USA and classifies all diseases and procedures. The ICD-9 diagnosis is matched with the corresponding CPT service codes to obtain reimbursement.

For inpatient hospital services the ICD-9 code is grouped with the CPT codes under a common Diagnosis Related Group (DRG) code. Under the DRG payment system the 20,000 or more ICD-9 codes have been grouped into a smaller category of 500 DRG codes and the payment for each DRG code is fixed based on diagnosis and is independent of length of stay. DRG payment includes physician services, hospital stays cost of devices and procedures.

14.3 Payment

As shown in Error! Reference source not found., the manufacturer has to negotiate with the payers, the providers and the suppliers.

- The manufacturer has to convince the physicians and hospitals that their product will be valuable in the treatment of patients by increasing the quality of life and/or reducing treatment costs.
- The manufacturer has to negotiate with the payers to get the appropriate amount of reimbursement from them so that the providers will be willing to use the product.
- The manufacturer can directly sell the product to the provider or sell it through distributors or suppliers. If the manufacturer decides to sell the product through
distributors, it will have to negotiate with the distributor so that they will appropriately bundle and market their product.

![Diagram](image)

Figure 14.1: Reimbursement Payment Structure in the US

The process of reimbursement is very complex and must be started early so that all components are in place when the product enters the market. If reimbursement has not be set up, the products sales would suffer significantly, till appropriate reimbursement can be obtained

14.4 PediaStent Reimbursement
They have consulted with a few reimbursement specialists to determine what would be the best route for us to obtain payment. Since stenting is an established procedure in adults they can bill under the same CPT and ICD-9 codes that are
currently being used for adults. Currently, coronary bare metal stents (BMS) are priced at or around $1000 and Drug Eluting Stents (DES) are priced at ~ $2500. In order to cover development costs as well as the small market size of pediatric patients, they plan to price PediaStent at $5000. This increased cost can be accommodated in one of two ways

- **Getting a new DRG code:** Johnson and Johnson was the pioneer in the DES technology. When they introduced their DES- CYPHER in 2003 they intended to price it at $3000. BMS’s in use at that time were being sold for $1000. In order to cover the additional costs, they worked with the CMS and obtained two new DRG codes that would cover the additional costs associated with CYPHER. J&J could accomplish this due to the various advantages that DES’s were believed to have compared to BMS.

- **Add-on hospital payment:** IN 2006, the CMS approved an add-on payment for St.Francis’ X STOP Interspinous Process Decompression System. The additional payment of $4400 would cover the cost of the device which offered a “substantial improvement over existing clinical treatment options.”

Carolyn Moora, a reimbursement specialist indicated that an add-on payment might be a feasible route if the device shows significant advantages over existing treatment options.

According to her, due the current financial conditions, recent statistics indicate that the payer mix (government versus private payers) is almost 50-50. In the past, most children were covered by private payers, but since many families are
at or near the poverty line, children are being increasingly covered by Medicaid. As a result, they will have to negotiate with the CMS as they'll the regional private payers to obtain reimbursement for the device.
15 SWOT Analysis

**Strengths**
- Non-profit company geared towards pediatrics has greater appeal with the clinical community
- Novel product – can control degradation as compared to competing products which have a fixed degradation time
- Niche and small market, so big pharmaceutical companies are not very interested. Keeps competition low
- Collaboration with a larger company who is developing the product for adults.
- Product development has been accomplished and data can be leveraged
- Physicians want this product; have been using off-the-shelf stents for years
- Can leverage the clinical and research strengths of the Cleveland region
- CEO has experience with startups

**Weaknesses**
- Company plans to stay small to maintain low overhead which can affect scaleup
- Small market will keep revenues low. Global expansion required for profits
- Licensing rights are with ART. This limits what PediaWorks can do with the product
- PediaWorks does not have in-house research or clinical capabilities and has to depend on other sources for this. Any changes with these sources can affect PediaWorks especially with timelines
- New usage of an old molecule. Associated problems and effects are unknown
- Currently very low on cash. Lack of in-house research staff precludes it from applying for SBA grants

**Opportunities**

- Product will create new therapy options where currently surgery is the gold standard
- Most competitors developing products for adults, no particular interest for the pediatrics market
- FDA focus on developing pediatric devices. A pediatric bioabsorbable stent task force has been established
- Industry trends for adult stents moving towards bioabsorbable materials
- Large Asian markets (India, China, Japan) with similar or higher incidence of CHD
- Developing stents for other pediatric indications besides CHD

**Threats**

- A small fish in a large pond – large pharmas might decide to enter the pediatric market due to incentives being offered by the FDA
- Universal healthcare reform to be implemented in 2014 will require medical device companies to pay a 2.3% additional tax
- In US and Europe, CHD has decreased 40-50% over the last few years due to better therapies and awareness. This is a shrinking market
- Unstable economic environment in US and Europe could affect purchasing power
- Clinical trials might not yield expected results
- PediaWorks might not procure the required funds
- Pediaworks might not obtain rights to the technology for pediatric indications
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